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(54) Title: **METHOD AND COMPOSITION FOR SKIN LIGHTENING APPLYING CARBOXYLIC ACIDS**

(57) Abstract: A method and composition is provided for treating skin to achieve lightening by applying a composition that includes an anti-microbial agent, an alpha- and/or beta-hydroxy carboxylic acid and a sunscreen.

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## METHOD AND COMPOSITION FOR SKIN LIGHTENING APPLYING CARBOXYLIC ACIDS

The present invention relates to a method and composition  
5 for lightening the color of skin.

Ever since the first freckle or hyper-pigmented spot  
appeared on the human face, there has been demand for  
treatment. Historically treatments have involved  
10 preparations of mercury, plant extracts and even lemon  
juice. Bleaching of skin with ammoniated mercury and other  
salts of this metal are reported to be quite effective. Of  
course there are significant safety issues involved with  
mercurials.

15 Zinc peroxide has been utilized in anhydrous ointments as a  
bleaching agent. Monobenzyl ether of hydroquinone was  
marketed for its skin lightening effect but questions of  
safety also arose.

20 Ascorbic acid preparations, either pure or made from a  
natural material, such as lemon juice, have also been  
suggested as useful lightening agents. While seemingly  
entirely safe, they do not appear to be very effective.

25 U.S. Patent 4,096,240 (Mathur) discloses that niacin is  
effective for skin lightening. This material is postulated  
as operating by retarding melanin dispersion or distribution  
into the epidermis. Since unpleasant skin flushing occurs  
30 with niacin, the patent suggests the use of niacinamide as a

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substitute. Compositions based upon niacinamide are effective, but only to a limited extent.

U.S. Patent 5,262,153 (Mishima *et al.*) reports the use of lactic acid and salts thereof as skin whitening agents. These must be used at concentrations of at least 5% in order to be effective. However, it is well known that alpha-hydroxy carboxylic acids, such as lactic acid, cause irritation to the skin, especially at higher levels of use.

U.S. Patent 5,482,710 (Slavtcheff *et al.*) reports the use of alpha and beta hydroxy carboxylic acids in combinations with salts of glycyrrhizinic acid, and anti-microbial agents including triclosan. These compositions were said to have anti-acne effectiveness reducing inflammation and pimples.

Accordingly, the present invention aims to provide a skin lightening composition and actives to accomplish this function which are more efficient than materials heretofore known and, additionally, are safe to use.

A method for lightening the color of skin is provided which includes applying to the skin a composition comprising:

- (i) from about 0.1 to about 15% by weight of an alpha- or beta- hydroxy carboxylic acid; and
- (ii) from about 0.01 to about 5% by weight of an anti-microbial agent; and
- (iii) a pharmaceutically acceptable carrier.

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A composition for skin lightening is also provided which includes:

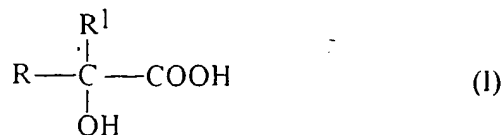
- (i) from about 0.1 to about 15% by weight of an alpha- or beta- hydroxy carboxylic acid;
- 5 (ii) from about 0.01 to about 5% by weight of an anti-microbial agent;
- (iii) from about 0.1 to about 30% by weight of a sunscreen agent; and
- (iv) a pharmaceutically acceptable carrier.

10

It has now surprisingly been discovered that alpha- and/or beta- hydroxy carboxylic acids in combination with anti-microbial agents can effectively lighten skin. The combination is effective against hyper-pigmentation, age spots and freckles. Use of the aforementioned components together should be incorporated into a regime that applies the compositions repeatedly to the same area of the skin. For instance, the composition may be applied daily for periods from several days to several weeks, before skin  
20 lightening becomes evident.

A first component of the compositions of the present invention is an alpha- and/or beta- hydroxy carboxylic acid. Illustrative of the beta-hydroxy carboxylic acids is  
25 salicylic acid. The alpha-hydroxy carboxylic acids are represented by formula I having the structure:

30



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wherein R and R<sup>1</sup> may be the same or different and are selected from H, F, Cl, Br, alkyl, aralkyl or aryl groups which may be saturated or unsaturated, isomeric or nonisomeric, straight or branched chain, having 1 to 25 carbon atoms, or in a cyclic form having 5 or 6 ring members. In addition, R and R<sup>1</sup> may be substituted with one or more OH, CHO, COOH or alkoxy groups having 1 to 9 carbon atoms. The alpha-hydroxy acid exists as a free acid, and includes stereoisomers, and D, L, and DL forms thereof when R and R<sup>1</sup> are not identical.

Illustrative of this group of materials are:

2-hydroxyethanoic acid (glycolic acid);  
2-hydroxypropanoic acid (lactic acid); 2-methyl 2-hydroxypropanoic acid (methyllactic acid); 2-hydroxybutanoic acid; 2-hydroxypentanoic acid; 2-hydroxyhexanoic acid; 2-hydroxyheptanoic acid; 2-hydroxyoctanoic acid; 2-hydroxynonanoic acid; 2-hydroxydecanoic acid; 2-hydroxyundecanoic acid; 2-hydroxydodecanoic acid (alpha-hydroxylauric acid); 2-hydroxytetradecanoic acid (alpha-hydroxymyristic acid); 2-hydroxyhexadecanoic acid (alpha-hydroxypalmitic acid); 2-hydroxyoctadecanoic acid (alpha-hydroxystearic acid); 2-hydroxyeicosanoic acid (alpha-hydroxyarachidonic acid); 2-phenyl 2-hydroxyethanoic acid (mandelic acid); 2,2-diphenyl 2-hydroxyethanoic acid (benzilic acid); 3-phenyl 2-hydroxypropanoic acid (phenyl lactic acid); 2-phenyl 2-methyl 2-hydroxyethanoic acid (atrolactic acid); 2-(4'-hydroxyphenyl) 2-hydroxyethanoic acid; 2-(4'-chlorophenyl 2-hydroxyethanoic acid; 2-(3'-

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- hydroxy-4'-methoxyphenyl) 2-hydroxyethanoic acid; 2-(4'-hydroxy-3'-methoxyphenyl)2-hydroxyethanoic acid; 3'-(2-hydroxyphenyl) 2-hydroxypropanoic acid; 3-(4'-hydroxyphenyl) 2-hydroxypropanoic acid; and 2-(3',4'-dihydroxyphenyl) 2-hydroxyethanoic acid.

Most preferred of this group of materials are glycolic acid, lactic acid and 2-hydroxyoctanoic acid or combinations thereof. Levels of alpha-hydroxy alkanolic acids may range from about 0.1 to about 10%, preferably between about 0.2 and 4%, optimally between about 0.4 and 1% by weight of the composition.

The term "acid" is intended to encompass salt forms such as ammonium, triethanolammonium, alkali and alkaline earth metal salts of the alpha- and beta- hydroxy carboxylic acids. Examples include potassium lactate, sodium lactate, potassium glycolate, sodium glycolate, ammonium lactate, ammonium glycolate and any combinations thereof.

In a particularly preferred embodiment, there will be present a mixture of both a beta-hydroxy carboxylic acid and an alpha-hydroxy carboxylic acid. For instance, the optimum combination is a mixture of salicylic acid and lactic acid in a relative weight ratio from about 20:1 to about 1:20, preferably from about 10:1 to 1:1, optimally from about 3:1 to about 2:1.

As used herein, the term "anti-microbial agent" refers to a wide variety of substances having germicidal action, such as the halogenated salicylanilides, halogenated carbanilides,

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halogenated bisphenols, alkylbenzoylacrylates, quaternary ammonium compounds, thiuram sulfides, dithiocarbamates, antibiotics, halogenated diphenyl ethers, halogenated anilides of thiophene carboxylic acids, and chlorhexidines.

5

Suitable halogenated salicylanilides include the following:

- 5-bromo-salicylanilide;
- 4'-5-dibromo-salicylanilide;
- ( 10 3,4',5-tribromo-salicylanilide;
- 6-chloro-salicylanilide;
- 4',5-dichloro-salicylanilide;
- 3,4',5-trichloro-salicylanilide;
- 4',5-diiodo-salicylanilide;
- 15 3,4',5-triiodo-salicylanilide;
- 5-chloro-3'-trifluoromethyl-salicylanilide;
- 5-chloro-2'-trifluoromethyl-salicylanilide;
- 3,5-dibromo-3'-trifluoromethyl-salicylanilide;
- 3-chloro-4-bromo-4'-trifluoromethyl-salicylanilide;
- 20 2,5-dichloro-3-phenyl-salicylanilide;
- ( 3',5-dichloro-4'-methyl-3-phenyl-salicylanilide;
- 3'-5-dichloro-4'-phenyl-3-phenyl-salicylanilide;
- 3,3',5-trichloro-6'-(p-chlorophenoxy)-salicylanilide;
- 3',5-dichloro-5'-(p-bromophenoxy)-salicylanilide;
- 25 3,5-dichloro-6'-phenoxy-salicylanilide;
- 3,5-dichloro-6'-(o-chlorophenoxy)-salicylanilide;
- 5-chloro-6'-(o-chlorophenoxy)-salicylanilide;
- 5-chloro-6'-beta-naphthyloxy-salicylanilide;
- 5-chloro-6'-alpha-naphthyloxy-salicylanilide;
- 30 3,3',4-trichloro-5,6'-beta-naphthyloxy-salicylanilide.

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Halogenated carbanilides are represented by the 3,4,4'-trichloro-carbanilide and the 3,3',4-trichloro derivatives and by 3-trifluoromethyl-4,4'-dichlorocarbanilide.

5 Suitable bis-phenols include the following:

2,2'-methylenebis(4-chlorophenol);  
2,2'-methylenebis(4,5-dichlorophenol);  
2,2'-methylenebis(3,4,6-trichlorophenol);  
10 2,2'-thiobis(4,6-dichlorophenol);  
2,2'-diketobis(4-bromophenol);  
2,2'-methylenebis(4-chloro-6-isopropylphenol)  
2,2'-isopropylidenebis(6-sec-butyl-4-chlorophenol).

15 Suitable alkylbenzoyl acrylates comprise the sodium salts of alkylbenzoylacrylic acids wherein the alkyl portion has from about 6 to about 12 carbon atoms.

Examples of quaternary ammonium compounds include:

20 diisobutylphenoxyethoxyethylidimethylbenzylammonium  
chloride;  
N-methyl-N-(2-hydroxyethyl)-N-(2-hydroxydodecyl)-N-  
benzyl ammonium chloride;  
25 cetyl trimethylammonium bromide;  
stearyl trimethylammonium bromide;  
oleyl dimethylethylammonium bromide;  
lauryl dimethylchloroethoxyethylammonium chloride;  
lauryl dimethylbenzylammonium chloride;  
30 alkyl (C<sub>8</sub>-C<sub>18</sub>)dimethyl(3,4-dichlorobenzyl)ammonium  
chloride;



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lauryl pyridinium bromide;  
lauryl isoquinolinium bromide;  
N-(lauroyloxyethylaminoformylmethyl)pyridinium chloride.

5 Examples of suitable thiocarbamates and thiuram sulfides include:

( 10 disodium ethylene bis-dithiocarbamate (nabam);  
diammonium ethylene bis-dithiocarbamate (amabam);  
Zn ethylene bis-dithiocarbamate (ziram);  
Fe ethylene bis-dithiocarbamate (ferbam);  
Mn ethylene bis-dithiocarbamate (manzate);  
tetramethyl thiuram disulfide;  
tetrabenzyl thiuram disulfide;  
15 tetraethyl thiuram disulfide;  
tetramethyl thiuram sulfide.

From the viewpoint of safety and effectiveness preferred antibacterial agents include:

20 ( 4',5-dibromosalicylanilide;  
3,4',5-tribromosalicylanilide;  
3,4',5-trichlorosalicylanilide;  
3,4,4'-trichlorocarbanilide;  
25 3-trifluoromethyl-4,4'-dichlorocarbanilide;  
2,2'-methylenebis(3,4,6-trichlorophenol);  
2,4,4'-trichloro-2'-hydroxydiphenyl ether;  
Tyrothricin;  
N-methyl-N-(2-hydroxyethyl-N-(2-hydroxydodecyl)-N-  
30 benzylammonium chloride.

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Especially preferred are:

2,3',5-tribromosalicylanilide;  
chlorohexidine digluconate;  
5 chlorohexidine diacetate;  
4',5-dibromosalicylanilide;  
3,4,4'-trichlorocarbanilide;  
2,4,4'-trichloro-2-hydroxydiphenyl ether.

- 10 Amounts of the anti-microbial agent may range from about ( 0.01 to about 5%, preferably from about 0.05 to about 3%, more preferably from about 0.1 to about 1%, optimally from about 0.2 to about 0.6% by weight of the composition.
- 15 In a further aspect of the invention, the action of the skin lightening composition is ensured against reversal of melanisation by the presence of an ultraviolet absorbing sunscreen in the composition. By the term "sunscreen" is meant any material, whether organic or inorganic, which can
- 20 shield the skin from ultraviolet radiation within the range of 290 to 400 nm. (

When the sunscreen is an organic material, it will usually contain at least one chromophoric agent absorbing within the

25 ultraviolet range somewhere from 290 to 400 nm. Chromophoric organic sunscreen agents may be divided into the following categories (with specific examples) including: p-aminobenzoic acid, and salts and derivatives thereof (ethyl, isobutyl, glyceryl esters; p-dimethylaminobenzoic

30 acid); Anthranilates (o-aminobenzoates; methyl, phenyl, benzyl, phenylethyl, linalyl, terpinyl, and cyclohexenyl

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esters); Salicylates (octyl, amyl, phenyl, benzyl, methyl, glyceryl, and dipropyleneglycol esters); Cinnamic acid derivatives (menthyl and benzyl esters, alpha-phenyl cinnamionitrile; butyl cinnamoyl pyruvate); Dihydroxycinnamic acid derivatives (umbelliferone, methylumbelliferone, methylacetoumbelliferone); Trihydroxycinnamic acid derivatives (esculetin, methylesculetin, daphnetin, and the glucosides, esculin and daphnin); Hydrocarbons (diphenylbutadiene, stilbene); Dibenzalacetone and benzalacetophenone; Naphtholsulfonates (sodium salts of 2-naphthol-3,6-disulfonic and of 2-naphthol-6,8-disulfonic acid); Dihydroxy-naphthoic acid and salts thereof; o- and p-Hydroxybiphenyldisulfonates; Coumarin derivatives (7-hydroxy, 7-methyl, 3-phenyl); Diazoles (2-acetyl-3-bromoindazole, phenyl benzoxazole, methyl naphthoxazole, various aryl benzothiazoles); Quinine salts (bisulfate, sulfate, chloride, oleate and tannate); Quinoline derivatives (7-hydroxyquinoline salts, 2-phenylquinoline); Hydroxy-or methoxy-substituted benzophenones; Uric and vilouric acids; Tannic acid and derivatives thereof (e.g. hexaethylether); (Butyl carbityl) (6-propyl piperonyl) ether; Hydroquinone; Benzophenones (Oxybenzone, Sulisobenzene, Dioxybenzone, Benzoescorcinol, 2,2',4,4'-Tetrahydroxybenzophenone, 2,2'-Dihydroxy-4,4'-dimethoxybenzophenone, Octabenzene; 4-isopropylidibenzoylmethane, Butylmethoxydibenzoylmethane; Etocrylene; and 4-isopropyl-dibenzoylmethane).

Particularly useful are: 2-ethylhexyl p-methoxycinnamate, 4,4'-t-butyl methoxydibenzoylmethane, 2-hydroxy-methoxybenzophenone, octyldimethylol p-aminobenzoic acid,

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digalloyltriolate, 2,2-dihydroxy-4-methoxybenzophenone,  
ethyl-4-[bis(hydroxypropyl)] aminobenzoate, 2-ethylhexyl-2-  
cyano-3,3-diphenylacrylate, 2-ethylhexylsalicylate, glyceryl  
p-aminobenzoate, 3,3,5-trimethylcyclohexylsalicylate,  
5 methylanthranilate, p-dimethylaminobenzoic acid or  
aminobenzoate, 2-ethylhexyl p-dimethylaminobenzoate, 2-  
phenylbenzimidazole-5 sulfonic acid, 2-(p-  
dimethylaminophenyl)-5-sulfoniobenzoxazoic acid and mixtures  
thereof.

10

Suitable commercially available organic sunscreen agents are  
those identified in the following table:

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TABLE I

CTFA NAME	TRADE NAME	SUPPLIER
Benzophenone-3	UVINUL M-40	BASF Chemical Co.
Benzophenone-4	UVIN UL MS-40	BASF Chemical Co.
Benzophenone-8	SPECTRA-SORB UV-24	American Cyanamid
DEA-Methoxycinnamate	BERNEL HYDRO	Bernel Chemical
Ethyl dihydroxypropyl-PABA	AMERSCREEN P	Amerchol Corp.
Glyceryl PABA	NPA G.M.P.A.	Nipa Labs.
Homosalate	KENESTER HMS	Hunko Chemical
Menthyl anthranilate	SUNAROME UVA	Felton Worldwide
Octocrylene	UVINUL N-539	BASF Chemical Co.
Octyl dimethyl PAPA	AMERSCOL	Amerchol Corp.
Octyl methoxycinnamate	PARSON MCX	Bernel Chemical
Octyl salicylate	SUNAROME WMO	Felton Worldwide
PABA	PABA	National Starch
2-Phenylbenimidazole-5-sulphonic acid	EUSOLEX 6300	EM Industries
TEA salicylate	SYBARINE W	Felton Worldwide
2-(4-Methylbenzilidene)-camphor	EUSOLEX 6300	EM Industries
Benzophenone-1	UVINUL 400	BASF Chemical Co.
Benzophenone-2	UVINUL D-50	BASF Chemical Co.
Benzophenone-6	UVINUL D-49	BASF Chemical Co.
Benzophenone-12	UVINUL 408	BASF Chemical Co.
4-Isopropyl dibenzoyl methane	EUSOLEX 8020	EM Industries
Butyl Methoxy dibenzoyl methane	PARSOL 1789	Givaudan Corp.
Etocrylene	UVINUL N-35	BASF Chemical Co.

Inorganic sunscreen actives may also be employed such as microfine titanium dioxide, zinc oxide, polyethylene, polyamides (e.g. nylon) and various other polymers. Amounts of the sunscreen agents (whether organic or inorganic) will generally range from 0.1 to about 30%, preferably from 2 to 20%, optimally from 4 to 10% by weight of the composition.

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Compositions of the present invention utilize a pharmaceutically acceptable carrier. The carrier may either be aqueous, anhydrous or an emulsion. Preferably the compositions are aqueous, especially water and oil emulsions of the W/O or O/W variety. Water, when present, will be in amounts which may range from 5 to 95%, preferably from 20 to 70%, optimally between 35 and 60% by weight of the composition.

10 In addition to water, relatively volatile solvents may also serve as suitable carriers for the compositions of the present invention. Most preferred are monohydric C<sub>1</sub>-C<sub>3</sub> alkanols, such as ethyl alcohol, methyl alcohol and isopropyl alcohol. The amount of monohydric alkanol may  
15 range from 1 to 70%, preferably from 10 to 50%, optimally between 15 to 40% by weight of the composition.

Emollient materials may also serve as pharmaceutically acceptable carriers. These may be in the form of silicone  
20 oils or synthetic esters. Amounts of the emollients may range anywhere from 0.1 to 30%, preferably between 1 and 20% by weight of the composition.

Silicone oils may be divided into volatile and nonvolatile  
25 silicone oils. The term "volatile" as used herein refers to those materials which have a measurable vapour pressure at ambient temperature. Volatile silicone oils are preferably chosen from cyclic or linear polydimethylsiloxanes containing from 3 to 9, preferably from 4 to 5 silicon  
30 atoms.

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Linear volatile silicone materials generally have viscosities of less than about 5 centistokes at 25°C, while cyclic materials typically have viscosities of less than about 10 centistokes.

5

Nonvolatile silicone oils which are useful as an emollient material for the compositions of the present invention include polyalkyl siloxanes, polyalkylaryl siloxanes and polyether siloxane copolymers. Suitable nonvolatile

( 10 polyalkyl siloxanes include, for example, polydimethyl siloxanes with viscosities ranging from about 5 to about 100,000 centistokes at 25°C. Among the preferred nonvolatile emollients useful in the present compositions are polydimethyl siloxanes having viscosities ranging from  
15 about 10 to about 400 centistokes at 25°C.

Suitable ester emollients include:

( 20 (1) alkenyl or alkyl esters of fatty acids having 10 to 20 carbon atoms, such as isoarachidyl neopentanoate, isononyl isonanonoate, oleyl myristate, oleyl stearate, and oleyl oleate;

( 25 (2) ether-esters such as fatty acid esters of ethoxylated fatty alcohols;

( 30 (3) polyhydric alcohol esters, such as ethylene glycol mono and di-fatty acid esters, diethylene glycol mono- and di-fatty acid esters, polyethylene glycol (200-6000) mono- and di-fatty acid esters, propylene glycol mono- and di-fatty acid ester, polypropylene glycol 2000 monooleate,

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polypropylene glycol 2000 monostearate, ethoxylated propylene glycol monostearate, glyceryl mono- and di-fatty acid esters, polyglycerol poly-fatty esters, ethoxylated glyceryl monostearate, 1,3-butylene glycol monostearate, 5 1,3-butylene glycol distearate, polyoxyethylene polyol fatty acid ester, sorbitan fatty acid esters, and polyoxyethylene sorbitan fatty acid esters;

(4) Wax esters such as beeswax, spermaceti, myristyl 10 myristate, stearyl stearate and arachidyl behenate;

(5) Sterols esters, of which cholesterol fatty acid esters are examples thereof.

15 Fatty acids having from 10 to 30 carbon atoms may also be included as pharmaceutically acceptable carriers for compositions of the present invention. Suitable examples include pelargonic, lauric, myristic, palmitic, stearic, isostearic, hydroxystearic, oleic, linoleic, ricinoleic, 20 arachidic, behenic and erucic acids, preferably stearic acid.

Amounts of the fatty acids may range from about 5 to about 50%, preferably from about 10 to about 25%, optimally from 25 about 12 to about 20% by weight of the composition. At levels of 5% or higher, the compositions may be considered as vanishing cream cosmetics.

Humectants of the polyhydric alcohol-type may also be 30 employed as suitable pharmaceutically acceptable carriers in compositions of the present invention. The humectant helps



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to increase the effectiveness of the emollients, reduces scaling, stimulates removal of built-up scale and generally improves skin feel. Typical polyhydric alcohols include glycerol, polyalkylene glycols and more preferably alkylene polyols and their derivatives, including propylene glycol, dipropylene glycol, polypropylene glycol, polyethylene glycol and derivatives thereof, sorbitol, hydroxypropyl sorbitol, hexylene glycol, 1,3-butylene glycol, isoprene glycol, 1,2,6-hexanetriol, ethoxylated glycerol, propoxylated glycerol and mixtures thereof. For best results the humectant is preferably propylene glycol. The amount of humectant may range anywhere from 0.5 to 30%, preferably between 1 and 15% by weight of the composition.

Thickeners may also be utilized as part of the pharmaceutically acceptable carrier of the compositions of the present invention. Typical thickeners include crosslinked acrylates (e.g. Carbopol®), hydrophobically-modified acrylates (e.g. Pemulen®), polyacrylamides (e.g. Sepigel 305), cellulosic derivatives and natural gums. Among useful cellulosic derivatives are sodium carboxymethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, ethyl cellulose and hydroxymethyl cellulose. Natural gums suitable for the present invention include guar, xanthan, sclerotium, carrageenan, pectin, sclerotium and combinations thereof. Amounts of the thickener may range from 0.0001 to 5%, usually from 0.001 to 1%, optimally from 0.01 to 0.5% by weight of the composition.

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Collectively the water, solvents, silicones, esters, fatty acids, humectants and/or thickeners which constitute the pharmaceutically acceptable carrier will be present in amounts ranging from 1 to 99.9%, preferably from 80 to 99%  
5 by weight of the composition.

Cosmetic compositions of the present invention may be in any form. These forms may include emulsified systems such as lotions and creams, micro-emulsions, roll-on formulations,  
10 mousses, ointments (hydrophilic and hydrophobic), aerosol and non-aerosol sprays and pad-applied formulations.

Surfactants may also be present in the compositions of the present invention. The total concentration of the  
15 surfactant may range from 0.1 to 40%, preferably from 1 to 20%, optimally from 1 to 5% by weight of the composition.

The surfactant may be selected from anionic, nonionic, cationic or amphoteric actives. Particularly preferred  
20 nonionic surfactants are those with a C<sub>10</sub>-C<sub>20</sub> fatty alcohol or acid hydrophobe condensed with from 2 to 100 moles of ethylene oxide or propylene oxide per mole of hydrophobe; C<sub>2</sub>-C<sub>10</sub> alkyl phenols condensed with from 2 to 20 moles of alkylene oxide; mono- and di- fatty acid esters of ethylene  
25 glycol; fatty acid monoglyceride; sorbitan, mono- and di-C<sub>8</sub>-C<sub>20</sub> fatty acids; block copolymers (ethylene oxide/propylene oxide); and polyoxyethylene sorbitan as well as combinations thereof. Alkyl polyglycosides and saccharide fatty amides (e.g. methyl gluconamides) are also  
30 suitable nonionic surfactants.

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Preferred anionic surfactants include soap, alkyl ether sulfate and sulfonates, alkyl sulfates and sulfonates, alkylbenzene sulfonates, alkyl and dialkyl sulfosuccinates, C<sub>8</sub>-C<sub>20</sub> acyl isethionates, acyl glutamates, sarcosinates, 5 taurates, C<sub>8</sub>-C<sub>20</sub> alkyl ether phosphates and combinations thereof.

Preservatives may also desirably be incorporated into the compositions of the present invention to protect against the growth of potentially harmful microorganisms. Suitable traditional preservatives include alkyl esters of para-hydroxybenzoic acid. Other preservatives which have more recently come into use include hydantoin derivatives, propionate salts, and a variety of quaternary ammonium 15 compounds. Cosmetic chemists are familiar with appropriate preservatives and routinely choose them to satisfy the preservative challenge test and to provide product stability. Particularly preferred preservatives are phenoxyethanol, methyl paraben, propyl paraben, butyl paraben, imidazolidinyl urea, sodium dehydroacetate and 20 benzyl alcohol. The preservatives should be selected having regard for the use of the composition and possible incompatibilities between the preservatives and other ingredients in the emulsion. Preservatives are preferably employed in amounts ranging from 0.01% to 2% by weight of 25 the composition.

The compositions of the present invention may have a pH ranging from about 1 to about 8.5, but preferably on the

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acidic side with a range from about 2 to about 6.5, preferably from about 3 to about 5.5.

Minor adjunct ingredients may also be present in the compositions. Among these may be water-insoluble vitamins such as Vitamin A Palmitate, Vitamin E Acetate and DL-panthenol.

Colorants, fragrances, opacifiers and abrasives may also be included in compositions of the present invention. Each of these substances may range from about 0.05 to about 5%, preferably between 0.1 and 3% by weight of the composition.

Except in the operating and comparative examples, or where otherwise explicitly indicated, all numbers in this description indicating amounts of material are to be understood as modified by the word "about".

#### EXAMPLES 1-8

The following examples are illustrative of vanishing cream type formulations according to the present invention. These formulations are capable of lightening skin.

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Vanishing Cream

COMPONENTS	EXAMPLE							
	1	2	3	4	5	6	7	8
Stearic Acid	15.00	15.00	10.00	10.00	10.00	25.00	25.00	5.00
Methyl Glucose Sesquistearate	2.25	3.00	2.00	2.00	2.25	3.25	4.00	1.00
Lactic Acid	1.00	--	2.92	--	6.67	1.67	2.37	3.50
Glycolic Acid	--	1.00	--	3.00	--	--	--	--
Cetyl Palmitate	1.20	1.20	6.20	7.20	1.20	1.20	1.20	1.20
Salicylic Acid	1.00	1.00	1.00	1.00	1.00	1.00	2.00	3.00
Methyl Stearate	0.57	0.57	0.57	0.57	0.57	0.57	0.57	0.57
Myristic Acid	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Benzoic Acid	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Perfume	0.23	0.23	0.23	0.23	0.23	0.23	0.23	0.23
Triclosan	0.20	0.40	--	--	--	0.20	--	0.10
Tricarbanilide	--	--	0.20	--	0.20	--	0.20	--
Chlorohexidine Digluconate	--	--	--	0.20	--	--	--	--
Methyl Paraben	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
Dipotassium Glycyrrhizinate	0.15	0.15	0.15	0.15	0.15	0.15	0.15	0.15
Silicone DC 200	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
Witch Hazel Extract	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Propyl Paraben	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Water	Bal.	Bal.	Bal.	Bal.	Bal.	Bal.	Bal.	Bal.

EXAMPLE 9

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A clinical trial was conducted to evaluate the efficacy of the compositions of the invention.

The study was conducted in collaboration with the Dermatology Department, Faculty of Medicine, University of Gadjah Mada, Jogjakarta. The method was a randomized, double blind, monadic, vehicle controlled, 12 week use test of various prototype formulations on the face. Subjects were required to come to the test site for a prescreen visit to determine facial baseline. The selected subjects were required to make six additional visits to the test site over a twelve-week period. At baseline (week 0), week 1, 2, 4, 8

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and 12, a variety of skin conditions including hyperpigmentation were evaluated by expert assessors (dermatologists). Subjects were asked to wash their face with soap and apply the test products at home, twice daily (morning and evening) and maintain a product use diary. Five cells with 60 females (aged 16-26 years old) per cell were randomly assigned to treatment groups. Four of the five groups were treated with experimental formulas containing test active ingredients. The fifth group received a cream base placebo. The active ingredients were formulated in a composition essentially equivalent to that described under Example 1, except that each of the four test products contained different amounts of the actives as indicated in Table I below.

**TABLE I**

Product***	Hyperpigmentation		
	Mean reduction (product) - mean reduction (placebo)		
	Week 4	Week 8	Week 12
2 SA + 1 LA	-0.2	0.65	-1.23
2 SA + 1 LA + TCN	6.28**	5.43*	5.2*
1 SA + 1 LA	1.18	0.22	-3.2
1 SA + 1 LA + TCN	5.54**	3.63	2.36

\* significantly different from placebo at  $p < 0.1$

\*\* significantly different from placebo at  $p < 0.05$

\*\*\* 1SA = 1% salicylic acid

2SA = 2% salicylic acid

1LA = 1% lactic acid

TCN = 0.2% Triclosan

It is clearly evident from these results that a combination of alpha- and/or beta- hydroxycarboxylic acids with triclosan was effective in significantly reducing hyperpigmentation.

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**EXAMPLE 10**

A micro-emulsion formulation according to the present invention is outlined in Table II.

5

**TABLE II**

INGREDIENT	WEIGHT (%)
Isodecyl Neopentanoate	16.00
SD Alcohol 40	12.00
Polyglyceryl-10 Decaoleate	10.50
PEG-8 Caprylic/capric Glycerides	10.50
Glyceryl Trioctanoate	8.00
DC Silicone Fluid 344®	8.50
PPG-5-Ceteth-20	4.00
Parsol MCX®	4.00
Acetaminophen	3.75
Isostearic Acid	2.50
Salicylic Acid	2.00
PEG-40 Hydrogenated Castor Oil	1.75
Lactic Acid	1.00
Phenoxyethanol	0.30
Tocopheryl Acetate	0.25
Triclosan	0.20
Propylparaben	0.15
Hydroxycaprylic Acid	0.10
Deionized Water	Q.S

**EXAMPLE 11**

A skin lotion (water in oil type) formulation according to the present invention is outlined under Table III.

5 **TABLE III**

INGREDIENT	WEIGHT (%)
Acetaminophen	6.00
Butylene Glycol	4.50
DC Silicone Fluid 344®	4.00
Parsol MCX®	4.00
Isononyl Isononanoate	3.75
Cetyl Dimethicone	2.50
Dimethicone Copolyol	2.50
Salacos HS®	2.50
Isostearic Acid	2.50
Octyl Octanoate	2.00
Salicylic Acid	2.00
Squalane	1.75
Glycerin	1.50
DC Silicone Fluid 200® (20 CST)	1.25
Zinc Myristate	1.25
Lactic Acid	1.00
Sodium Hyaluronate	1.00
Tocopheryl Acetate	0.55
Methylparaben	0.20
Phenoxyethanol	0.20
Triclosan	0.40
Hydroxycaprylic Acid	0.10
Propylparaben	0.10
Deionized Water	Q.S



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EXAMPLE 12

A skin cream (oil in water type) with sunscreen formulation according to the present invention is outlined in Table IV.

TABLE IV

INGREDIENT	WEIGHT (%)
Acetaminophen	5.00
Stearic Acid	3.50
Butylene Glycol	3.00
Parsol MCX®	3.00
Parsol 1789®	3.00
Cetyl/Stearyl Alcohol	2.55
Glycerin	2.50
Isostearyl Isononanoate	2.25
Sodium PCA	2.10
Glycolic Acid	2.00
Glycereth-7 Hydroxystearate	1.50
Triethanolamine	1.50
Glyceryl Hydroxystearate	1.25
Cocoa Butter	1.25
DC Silicone Fluid 200® (50 CST)	1.25
Steareth-20	1.20
Squalene	1.05
Salicylic Acid	1.00
Magnesium Aluminum Silicate	0.75
DC Silicone Fluid 200® (100 CST)	0.50
Hydroxyethylcellulose	0.50
Sodium Hyaluronate	0.50
Tocopherol	0.35
Glydant®	0.30
Methylparaben	0.20
Triclosan	0.10
Propylparaben	0.10
Disodium EDTA	0.05
Deionized Water	Q.S

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**EXAMPLE 13**

An anhydrous system with an inorganic (titanium dioxide) sunscreen formulation according to the present invention is outlined under Table V.

**TABLE V**

INGREDIENT	WEIGHT (%)
Isononyl Isononanoate	30.00
SD Alcohol 40 (200°)	20.00
Zinc Oxide	8.00
DC Silicone Fluid 200® (10 CST)	5.25
Acetaminophen	2.75
Dimethiconol	2.50
Octyl Isononanoate	2.25
Squalene	1.05
Butylene Glycol	1.00
Tocopheryl Linoleate	0.50
Salicylic Acid	0.50
Lactic Acid	0.50
Triclosan	0.20
Propylparaben	0.10
Tocopheryl Acetate	0.10
DC Silicone Fluid 344®	QS

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EXAMPLE 14

A skin lotion (oil in water type) formulation according to the present invention is outlined in Table VI.

TABLE VI

INGREDIENT	WEIGHT (%)
Acetaminophen	3.50
Coco Caprylate/Caprate	3.25
Lactic Acid	3.00
Salicylic Acid	3.00
Parsol MCX®	3.00
Butylene Glycol	3.00
Squalene	2.25
DEA-Cetyl Phosphate	2.15
Sodium PCA	2.10
Glycerin	2.00
Shea Butter Glycerides	1.25
Steareth-20	1.20
Cetyl Alcohol	1.00
Saccharide Isomerate	1.00
Magnesium Aluminum Silicate	0.75
DC Silicone Fluid 200® (50 CST)	0.75
DC Silicone Fluid 200® (50 CST)	0.50
Sucrose Laurate	0.50
Ceteth-2	0.50
Sodium Hyaluronate	0.35
Xanthan Gum	0.20
Methylparaben	0.20
Propylparaben	0.10
Germall II®	0.30
Tocopheryl Acetate	0.20
Triclosan	0.20
Disodium EDTA	0.05
Deionized Water	Q.S

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EXAMPLE 15

A protective skin lotion with sunscreen formulation according to the present invention is outlined in Table VII.

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**TABLE VII**

INGREDIENT	WEIGHT (%)
Parsol MCX®	6.00
Lactic Acid	4.00
Propylene Glycol Dicaprylate/Dicaprate	3.55
Benzophenone-3	3.00
Butylene Glycol	3.00
Acetaminophen	3.00
Coco Caprylate/Caprate	2.25
Squalene	2.00
Salicylic Acid	2.00
Aloe Vera Gel	2.00
Sepigel 305®	1.50
Shea Butter	1.50
DEA-Cetyl Phosphate	1.25
Ceteareth-20	1.20
DC Silicone Fluid 200® (350 CST)	1.00
Glycerin	1.00
Cetyl Alcohol	1.00
Xanthan Gum	0.15
DC Silicone Fluid 200® (20 CST)	0.50
Ceteth-2	0.50
Sodium Hyaluronate	0.35
Methylparaben	0.30
Tocopheryl Acetate	0.30
Triclosan	0.20
Glydant®	0.20
Propylparaben	0.15
Disodium EDTA	0.05
Deionized Water	Q.S

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The foregoing description and examples illustrate selected embodiments of the present invention. In light thereof variations and modifications will be suggested to one skilled in the art, all of which are within the spirit and  
5 purview of this invention.



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CLAIMS

1. A method for lightening the color of skin comprising applying the skin a composition comprising:

- 5           (i)    from about 0.1 to about 15% by weight of an  
              alpha- or beta- hydroxy carboxylic acid;  
              (ii) from about 0.01 to about 5% by weight of an  
                  anti-microbial agent; and  
              (iii) a pharmaceutically acceptable carrier.

( 10       2. A method according to claim 1 wherein the alpha-hydroxy  
          carboxylic acid is selected from glycolic acid, lactic acid,  
          2-hydroxyoctanoic acid or combinations thereof.

15       3. A method according to claim 1 or claim 2 wherein the  
          beta-hydroxy carboxylic acid is salicylic acid.

          4. A method according to any one of the preceding claims  
          wherein the skin lightening composition removes age spots  
20       and freckles, or eliminates hyperpigmentation.

(       5. A method according to any one of the preceding claims  
          wherein the anti-microbial agent is 2,4,4'-trichloro-2-  
          hydroxydiphenyl ether.

25

6. A cosmetic composition comprising:

- (i)    from about 0.1 to about 15% by weight of an alpha-  
                  or beta- hydroxy carboxylic acid;  
          (ii) from about 0.01 to about 5% by weight of an anti-  
30       microbial agent;

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- (iii) from about 0.1 to about 30% by weight of a sunscreen agent; and
- (iv) a pharmaceutically acceptable carrier.

5 7. A composition according to claim 6 wherein the anti-microbial agent is 2,4,4'-trichloro-2-hydroxydiphenyl ether.

8. A composition according to claim 6 or claim 7 wherein the alpha-hydroxy carboxylic acid is selected from  
10 glycolic acid, lactic acid, hydroxyoctanoic acid or (combinations thereof.

9. A composition according to any one of claims 6 to 8 wherein the beta-hydroxy carboxylic acid is salicylic acid.

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10. A composition according to any one of claims 6 to 9 wherein component (ii) comprises a mixture of both an alpha- and a beta- hydroxy carboxylic acid.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/02459

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 58628 A (MARY KAY INC) 30 December 1998 (1998-12-30) examples	1-4, 6, 8, 9
X	US 5 482 710 A (SLAVTCHEFF CRAIG S ET AL) 9 January 1996 (1996-01-09) cited in the application example 5	6-10
A	DATABASE WPI Section Ch, Week 199846 Derwent Publications Ltd., London, GB; Class D16, AN 1998-535017 XP002170880 & JP 10 234356 A (ATSUNARI SANGYO KK), 8 September 1998 (1998-09-08) abstract	1-10

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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